Tenth Annual Report 2001

Creutzfeldt-Jakob Disease Surveillance in the UK

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Summary

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Surveillance Unit (NCJDSU) became a WHO Collaborative Centre for Reference and Research on the Surveillance and Epidemiology of Human Transmissible Spongiform Encephalopathies (TSEs). In September 2001 the National Care Team was formed, comprising 2 care co-ordinators, a neurologist (part-time) and a secretary. The National Care Team is based within the NCJDSU and was formed in response to concerns regarding the care of CJD patients.

The information provided in this tenth report continues to provide evidence of a high level of case ascertainment. Detailed clinical and epidemiological information has been obtained for the great majority of patients and the case-control study for CJD has been extended for variant CJD, with up to 4 community controls studied in addition to the hospital controls. The post mortem rate for patients with suspected CJD is high, although there is recent evidence that the autopsy rates have declined, in line with autopsy rates in the UK generally following the Alder Hey Inquiry.

In 1990-2001 mortality rates from sporadic CJD in England, Scotland, Wales and Northern Ireland were, respectively, 0.77, 0.85, 1.03 and 0.52/million/year. The difference between the rates in each country is not statistically significant ($p>0.2$). These rates are comparable to those observed in other countries in Europe and elsewhere in the world, including countries which are free of BSE. There was some variation in the observed mortality rates between the different regions within the UK but this variation is not statistically significant ($p>0.2$). The highest and lowest mortality rates from sporadic CJD were observed in the South West (SMR=129) and East and West Midlands regions of England (both SMR=83).

Up to 31 December 2001, there have been 104 deaths from definite or probable variant CJD (vCJD) in the UK. Of these, 89 were confirmed neuropathologically with one additional case awaiting neuropathological confirmation. The clinical, neuropathological and epidemiological features of all these cases of vCJD are remarkably uniform and consistent with our previous descriptions. Analysis of the incidence of vCJD onsets and deaths from January 1994 to December 2001 shows evidence of an annual increase of around 20% for both onsets and deaths but, because of the considerable uncertainties over the incubation period for vCJD, continuing surveillance will be required to establish whether this trend is sustained in future years.

Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - 98 cases of vCJD with available genetic analysis have all been methionine homozygotes. The analyses in this report do not provide conclusive evidence of an increased risk of vCJD associated with past surgery, previous blood transfusion, occupation or a range of dietary factors. However, the power of the case-control study, from which these results are derived, is limited by the relatively small number of cases and controls. Cases of vCJD are reported to have consumed products potentially containing mechanically recovered meat (such as sausages and burgers) more frequently than community controls. However, care should be taken in interpreting this result as there is considerable scope for recall bias with respect to dietary history. The incidence of vCJD across the UK continues to show a "North-South" divide, with a higher incidence being maintained in the North of the UK. The underlying reason for this finding is not clear and further investigations are required to investigate the possible aetiology. The only statistically significant cluster of vCJD cases in the UK is in Leicestershire; geographically associated cases of vCJD are subject to detailed investigation, which involves the NCJDSU, colleagues at CDSC and local public health physicians.

The activities of the NCJDSU are strengthened by collaboration in other surveillance projects, including the Transfusion Medicine Epidemiology Review and the study of Progressive Intellectual and Neurological Deterioration in Children. The collaboration of our colleagues in these projects is greatly appreciated. The success of the project continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. We are particularly grateful to the relatives of patients for their help with this study.

SECTION

2

2. Clinical Surveillance

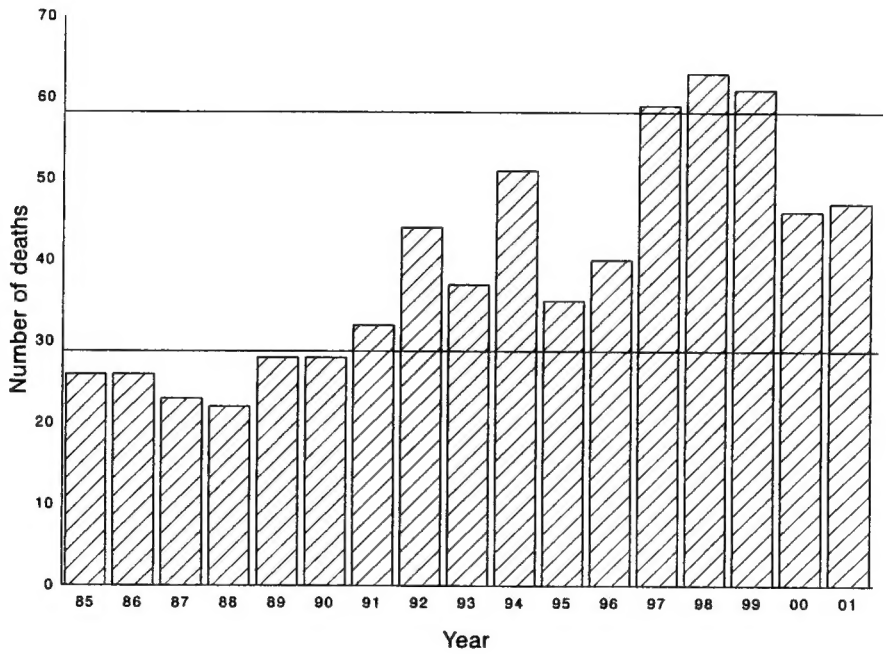
The national surveillance of CJD in the UK was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the NCJDSU was to identify any change in the pattern of CJD that might be attributable to the emergence of bovine spongiform encephalopathy (BSE). Such a change was recognised in 1996 when vCJD was first described. The NCJDSU now aims to monitor characteristics of CJD, specifically sporadic CJD and variant CJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings from the NCJDSU (UK) in relation to cases of sporadic, familial, iatrogenic and vCJD referred up to 31st December 2001 (with data ascertained up to 31st January 2002). Data from England and Wales include retrospective data from 1970; for Scotland and Northern Ireland retrospective data are available from 1985.

2.1 Sporadic Creutzfeldt-Jakob disease

Between 1st January 1970 and 31st December 2001, 944 cases of sporadic CJD were identified in the UK, of which 9 cases were still alive on 31st December 2001. Two further cases were identified in Jersey but they were not included in the following UK analyses. Of these UK cases, 730 (77%) were classified as definite cases with the remainder classed as probable. Figure 1a shows the number of deaths each year from sporadic CJD for the UK between 1985 and 2001, Figure 1b shows similar data for England and Wales between 1970 and 2001 and Figure 1c shows the number of deaths from sporadic CJD in Scotland and Northern Ireland between 1985 and 2001. In England and Wales the number of deaths identified each year has increased from an average of about 10 per year at the beginning of

the 1970s, to about 40 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are available for Scotland and Northern Ireland there is no clear secular trend. Over the period 1990-2001 the average crude annual mortality rates from sporadic CJD per million population were 0.77 in England, 1.03 in Wales, 0.85 in Scotland and 0.52 in Northern Ireland, as shown in Table 1. When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant ($p > 0.2$).

Figure 1a Deaths from sporadic CJD, UK, 1985-2001



Note:
1. The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 per million per year
2. Data for 2001 are not yet complete.

Figure 1b Deaths from sporadic CJD, England and Wales, 1970-2001

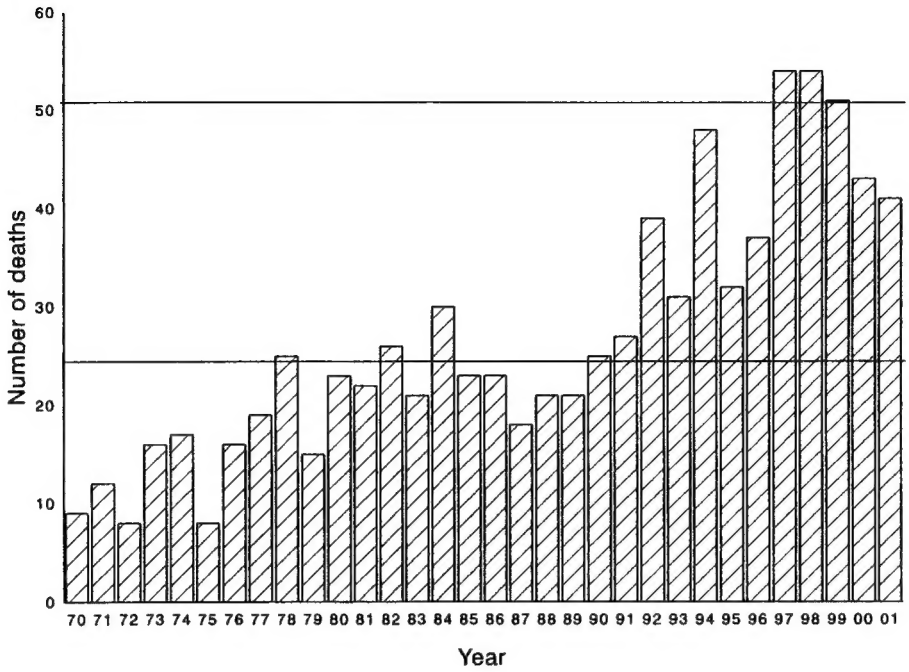
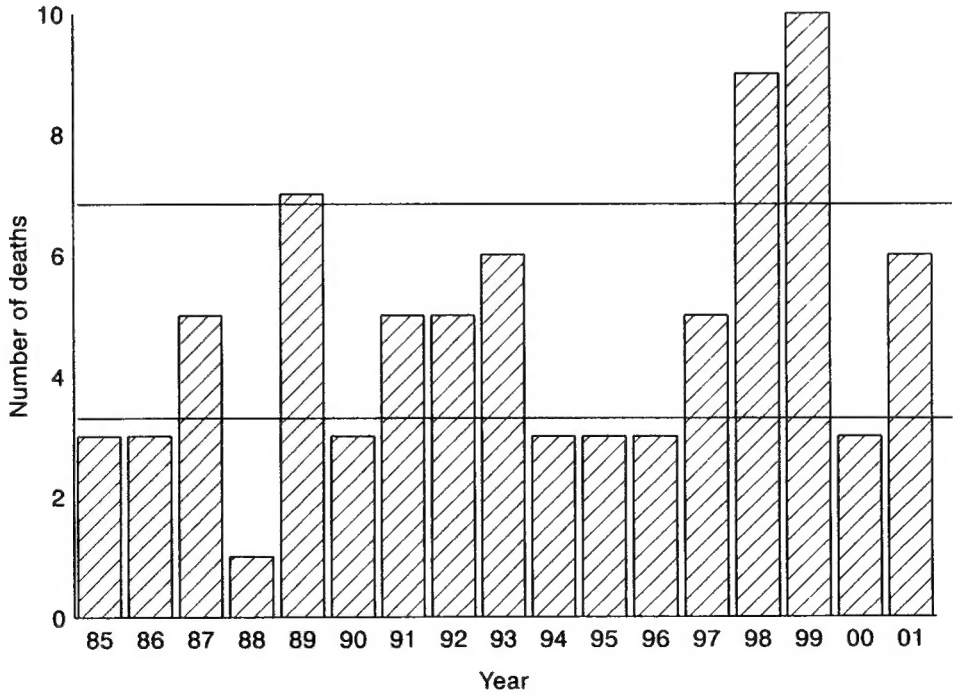


Figure 1c Deaths from sporadic CJD, Scotland and Northern Ireland, 1985-2001 (please note different scale from Figure 1b)



Note:
1. The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 per million per year
2. Data for 2001 are not yet complete.

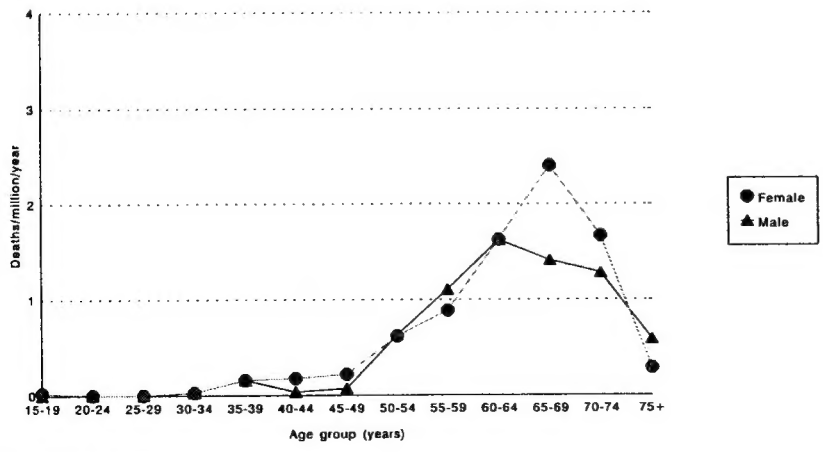
Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 01/05/1990 – 31/12/2001

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
North		
Cleveland	1	
Cumbria	9	
Durham	3	28 (0.77)
Northumberland	3	
Tyne & Wear	12	
East Midlands		
Derbyshire	5	
Leicestershire	11	
Lincolnshire	6	31 (0.65)
Northamptonshire	1	
Nottinghamshire	8	
South East		
Bedfordshire	5	
Berkshire	7	
Buckinghamshire	2	
East Sussex	6	
Essex	18	
Greater London	52	146 (0.70)
Hampshire	14	
Hertfordshire	5	
Isle of Wight	1	
Kent	11	
Oxfordshire	6	
Surrey	8	
West Sussex	11	
North West		
Cheshire	8	
Greater Manchester	22	61(0.82)
Lancashire	14	
Merseyside	17	
ENGLAND		
Yorkshire & Humberside		
Humberside	6	
NorthYorkshire	10	
South Yorkshire	13	45 (0.77)
West Yorkshire	16	
East Anglia		
Cambridgeshire	3	
Norfolk	9	23 (0.94)
Suffolk	11	
South West		
Avon	11	
Cornwall	7	
Devon	13	
Dorset	14	62 (1.11)
Gloucestershire	5	
Somerset	5	
Wiltshire	7	
West Midlands		
Hereford & Worcs.	3	
Shropshire	4	
Staffordshire	8	40 (0.65)
Warwickshire	2	
West Mids (Met)	23	
TOTAL FOR ENGLAND		**436 (0.77)**
WALES		
Clwyd	4	
Dyfed	4	
Gwent	5	
Gwynedd	6	
Mid Glamorgan	8	
Powys	2	
South Glamorgan	2	
West Glamorgan	4	
TOTAL FOR WALES		**35 (1.03)**
NORTHERN IRELAND	10	**10 (0.52)**
SCOTLAND		
Borders	2	
Central	5	
Dumfries & Galloway	0	
Fife	2	
Grampian	7	
Highland	1	
Lothian	13	
Strathclyde	18	
Tayside	1	
Islands (Shetland)	2	
Islands (Orkney)	0	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**51 (0.85)**

* Based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 11.67 year period of the study.

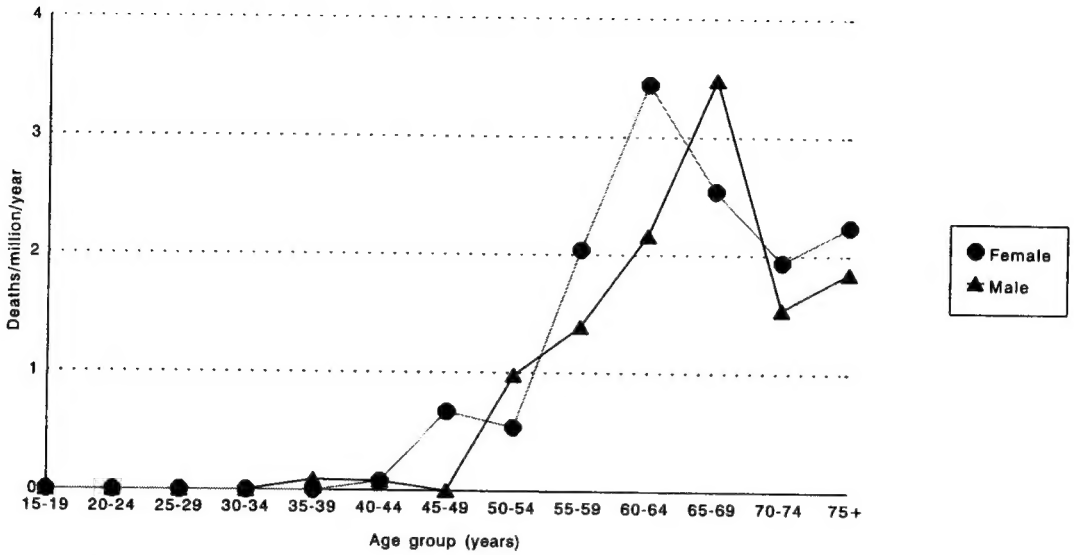
Figure 2a, 2b and 2c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-95 and 1996-01, respectively. The median ages of cases at death during these time periods were 64, 66 and 67 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.2/million/year). Thereafter, in all three periods, the mortality rates increased between the ages of 60-64 and 70-74 years and then declined. The age at height of the peak has tended to increase over time (peak mortality rates of 1.96 and 2.97 cases/million/year among 65-69 year olds during 1970-89 and 1990-95, respectively, and 3.76 cases/million/year among 70-74 year olds during 1996-01). The decline in mortality rate in the older age groups has become less marked over time. The mortality rate in those over 75 years of age was 3.04 cases/million/year in 1996-01, 2.11 cases/million/year in 1990-95 and 0.38 cases/million/year in 1970-89. These observed differences in the rates in the older age groups over the three time periods could be explained by an increase in case ascertainment over time. Another notable feature over the time period studied is a change in the sex ratio, affecting particularly older cases. In the earliest period there was a non-significant female excess (p=0.16), with similar male/female rates in 1990-1995 (p=0.17), but a male excess in 1996-2001 (p=0.02). The explanation for this trend is unclear. Prior to 1996 referral rates in males and females were similar across all age groups. Since 1996, referral rates in males aged 70+ appear to have increased substantially while in females aged 70+ referral rates appear largely unchanged from the period 1990-1995. The source of referral of male cases aged 70+ has not changed over time. In addition, the proportions of male and female referrals aged 65+ undergoing post mortem since 1996 are similar (74% in males versus 72% in females).

Figure 2a Age- and sex-specific mortality rates from sporadic CJD in the UK: 1970-1989
(NB: from 1970-1984 only England & Wales, thereafter UK)



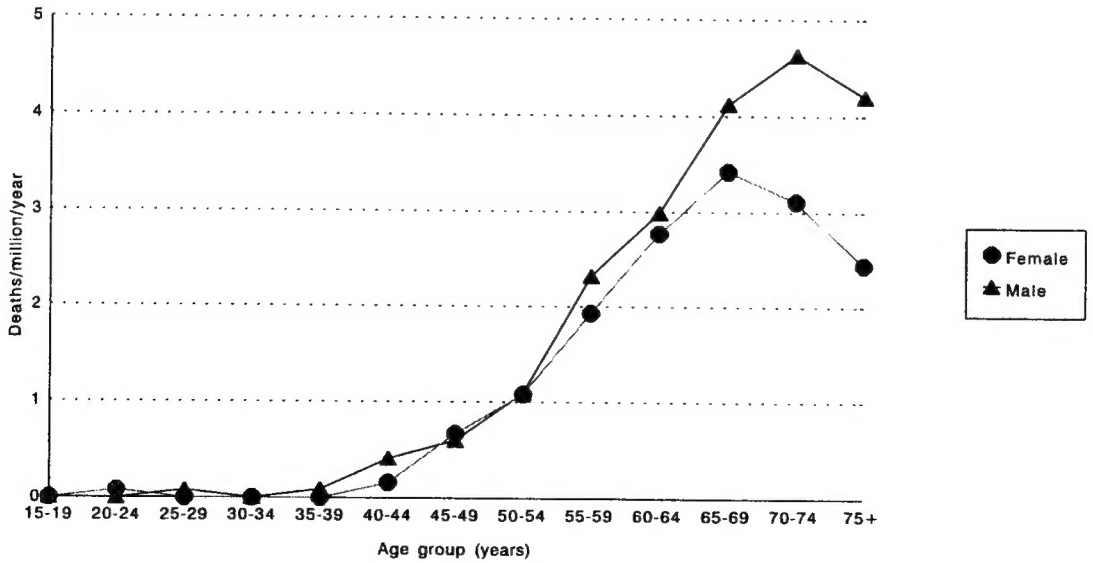
Mortality rates calculated using 1981 Census for GB and 1991 Census for NI

Figure 2b Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1995



Mortality rates calculcated using 1991 Census

Figure 2c Age- and sex-specific mortality rates from sporadic CJD in the UK 1996-2001



Mortality rates calculcated using 1991 Census

An analysis of age specific trends from 1970 to 2001 (Figure 3) shows there has been an increase in recorded mortality over time in all age groups, but that the greatest relative increase has occurred in those aged 70 years and above. Currently the mortality rate in this age group is similar to that in the age group 60-69 years. The temporal increases in mortality are statistically significant in all age groups $p=0.002$, $p=0.001$, $p<0.001$, $p<0.001$ in the age groups 40-49, 50-59, 60-69 and 70+ respectively. These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly.

Figure 3 Trends in mortality from sporadic CJD by age: 1970-2001

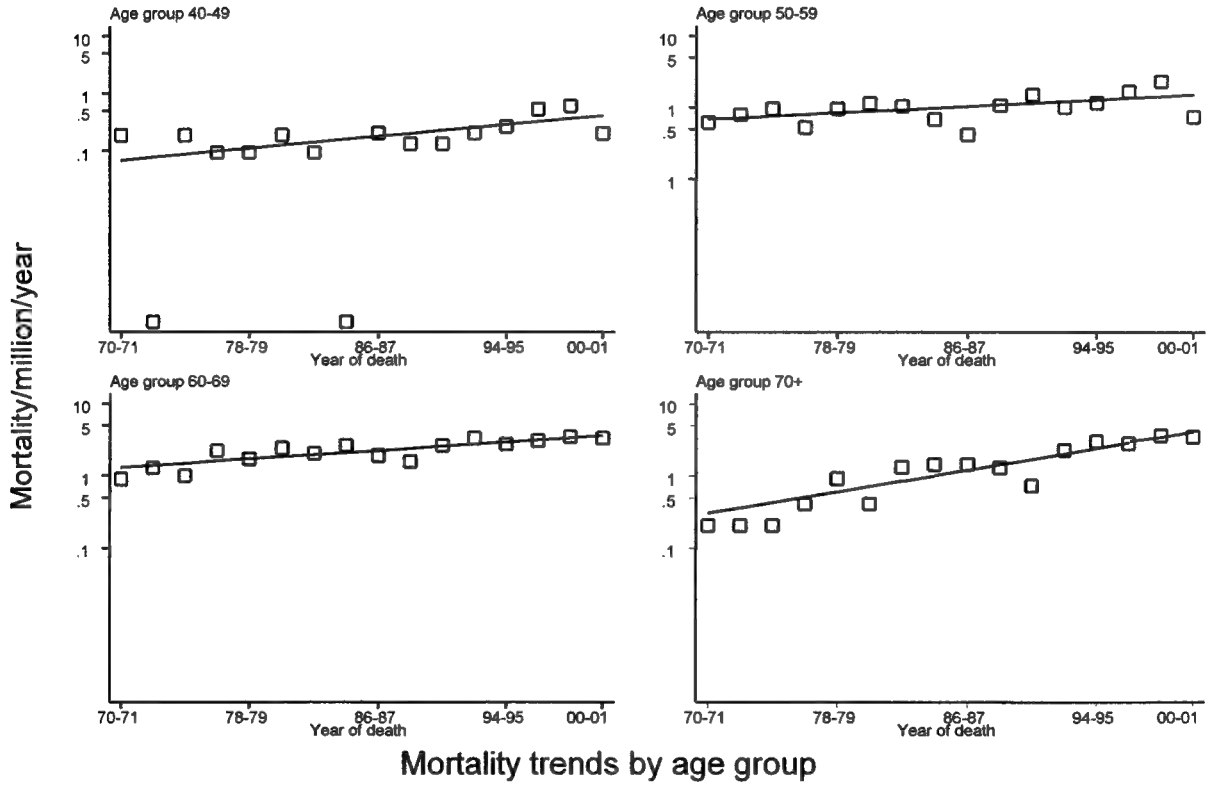


Table 2 presents, by 2-year period, the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged less than 50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 20 per year in the UK in recent years.

Table 2 Cases of sporadic CJD in England and Wales (from 1970) and the UK (from 1985) by two year period

Age at death (years)	Year of death																
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85[1]	86-87	88-89	90-91	92-93	94-95	96-97	98-99	00-01[2]	**Total[2]**
10-19	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	**1 (0)**
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	**2 (0)**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1	0	**14 (0)**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	9	3 (1)	**43 (1)**
50-59	7	9	11	6	11	13	12	8	5	13	18	12	14	20	28	9 (3)	**196 (3)**
60-69	9	13	10	22	17	24	20	28	22	18	30	38	31	35	40	38 (3)	**395 (3)**
70 +	2	2	2	4	9	4	13	16	18	16	9	28	37	35	45	43 (2)	**283 (2)**
Total	**21**	**24**	**25**	**35**	**40**	**45**	**47**	**56**	**49**	**50[3]**	**60**	**81**	**86**	**99**	**124**	**93 (9)**	**935[3] (9)**

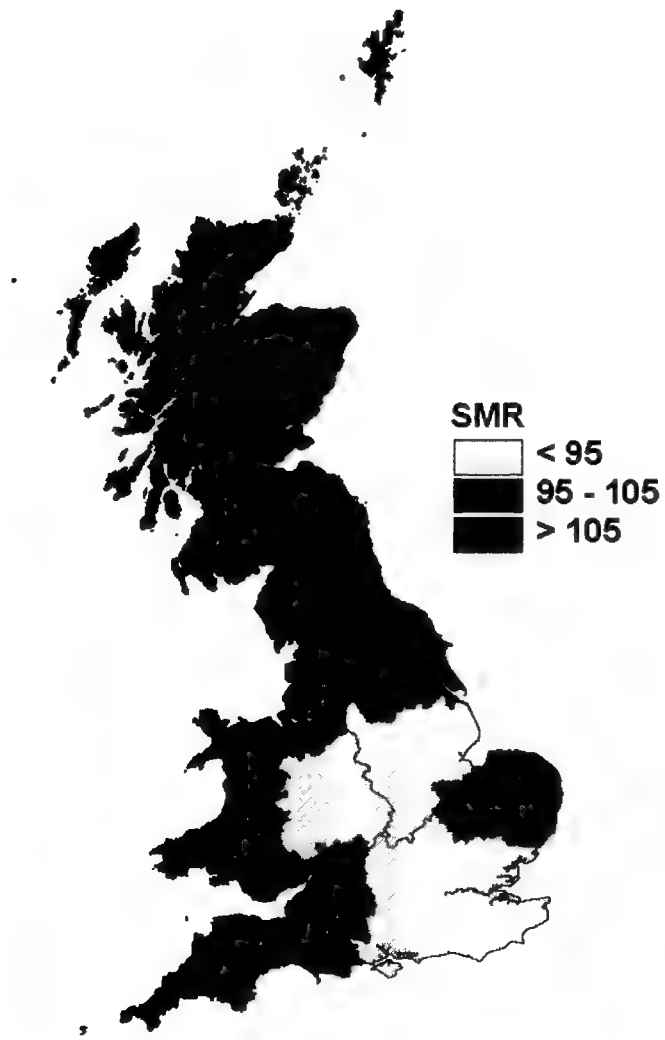
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included

[2] Deaths up to 31st December 2001. Numbers in parentheses indicate additional cases alive on 31st December 2001. Data for 2001 not yet complete.

[3] Total includes one case whose age at death was unknown

Age- and sex- standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st May 1990 to 31st December 2001 were calculated. Figure 4 shows the 10 regions of Great Britain. Northern Ireland has an SMR of 80. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p > 0.2$). Regions of relatively high mortality are South West (SMR=129), Wales (SMR=123) and East Anglia (SMR=115). Low mortality rates were observed in East and West Midlands (both SMR=83). The SMRs for the other five regions all lay between 94 and 109. The highest SMR (129 in South West) arose from 62 cases observed compared with 48 expected, an excess of about one case every year compared to the national average. In Wales and East Anglia the total numbers of excess cases were approximately 6 and 3 respectively.

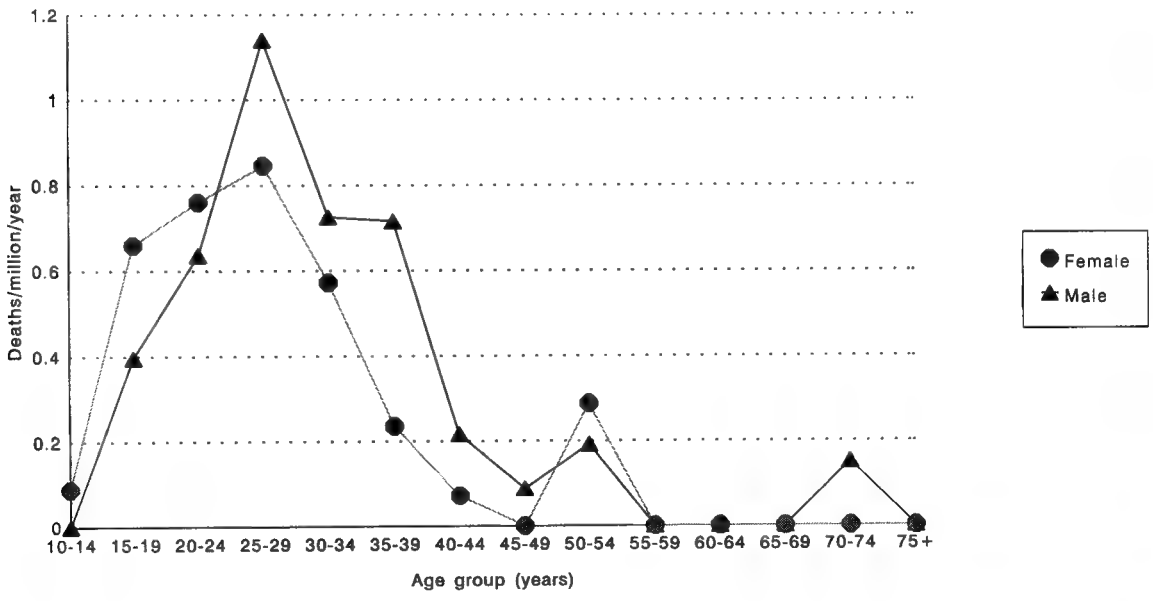
Figure 4 **Standardised mortality ratios (SMRs) by standard region, Great Britain, May 1990 - December 2001**



2.2 Variant Creutzfeldt-Jakob disease

Up to 31st January 2002, 114 cases of definite or probable vCJD had been identified in the UK (89 definite, one probable awaiting neuropathological confirmation, 15 probable who did not undergo post mortem and 9 probable cases still alive). Fifty-four (47%) of the 114 cases were women. The median age at onset of disease was 26 years and the median age at death 28 years (compared with 65 years for the median age at death for sporadic CJD). The youngest case was aged 12 years at onset while the oldest case was aged 74 years. The age- and sex-specific mortality rates for vCJD over the time period 1 May 1995 to 31 January 2002 are shown in Figure 5. The median duration of illness from the onset of first symptoms to death was 13 months (range 6-39). The comparable duration of illness for cases of sporadic CJD was 4 months (range 1 to 74) during the period 1990-2001.

Figure 5 Age- and sex-specific mortality rates from vCJD in the UK 1 May 1995 - 31 January 2002



Mortality rates calculcated using 1991 Census

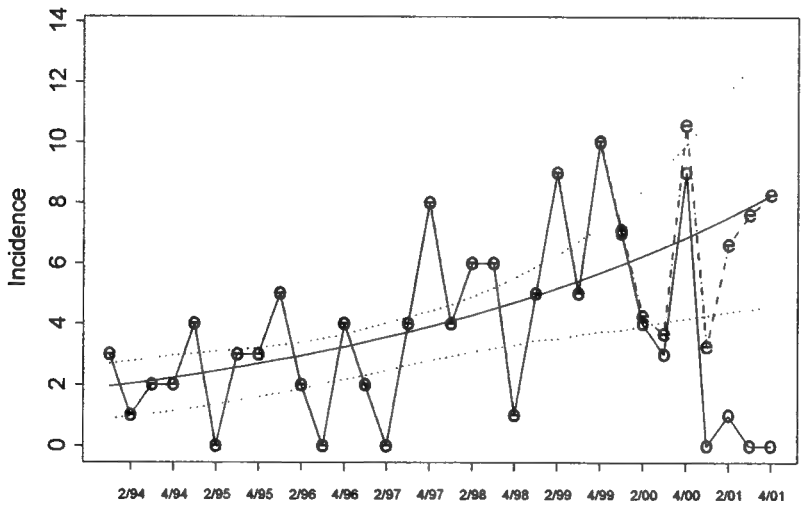
Incidence of vCJD onsets and deaths from January 1994 - December 2001

Each quarter the data on diagnosed cases of vCJD are reviewed in order to investigate trends in the underlying rate at which onsets and deaths are occurring. The following analysis reviews the data to the end of December 2001 by which time there was a total of 113 cases of which 104 had died. The data were grouped into quarters and modelled using Poisson regression.

Results for Onsets

Figure 6 shows the observed and expected number of onsets and the estimated trend (assuming exponential growth) with 95% confidence intervals (CIs).

Figure 6 Observed (-o-) and expected (-e-) quarterly incidence of vCJD onsets Fitted underlying trend*(__) is given with its 95% confidence limits (...)



* includes adjustment for delay from onset to diagnosis

On the basis of an exponential growth model the best estimate of annual increase in the number of cases is 21% with 95% confidence interval (9% to 34%) which is equivalent to a doubling every 3.7 years, 95% CI (2.4 – 7.9 years).

Since vCJD was first identified, the average interval between the onset of first symptoms and the diagnosis of vCJD has decreased. The mean delay to diagnosis is estimated to have reduced by 5% per year to an estimated current mean of 10 months from about 14 months at the end of 1995.

A model including a quadratic term did not give a significantly better fit (p=0.42) so there is no evidence of a departure from an exponentially increasing trend. The value for the quadratic term is, however, negative which is consistent with an epidemic reaching its peak. The data currently do not enable these two possibilities (continuing exponential increase or evidence of 'peaking') to be distinguished.

Predicted onsets by the end of December 2001

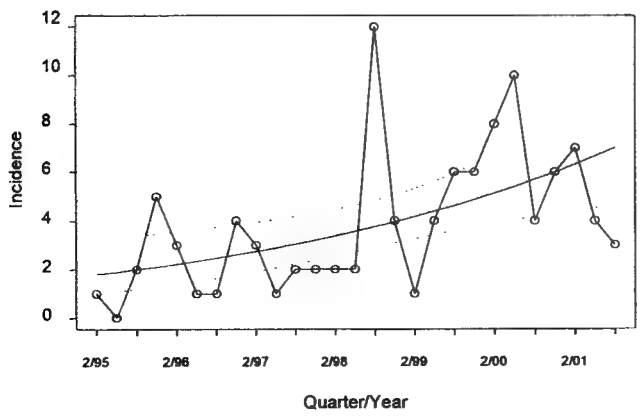
Based upon the exponential model, the total number of cases estimated to have had onsets by December 2001 is 140 (113 already diagnosed plus 27 not yet diagnosed) with a 95% CI of 131 to 154.

Results for Deaths

All deaths combined

Figure 7 shows the observed numbers of deaths by quarter with a fitted underlying exponential trend and 95% confidence interval.

Figure 7 Observed (-o-) quarterly incidence of vCJD deaths
Fitted underlying trend (___) is given with 95% confidence limits (...)



The estimated annual increase is 23% per year, 95% CI (8% to 41%). The estimate of the current quarterly number of deaths is 7.0. As with onsets, the model which included a quadratic term did not give a significantly better fit (p=0.20) so the data are consistent with a continuing exponentially increasing trend. The value for the quadratic term is, however, negative which is also consistent with an epidemic reaching its peak.

Prediction for deaths in the next 12 months

From the model, if the exponential trend continues, the predicted total number of deaths from January 2002 to December 2002 is 32 with a 95% confidence interval of 19 to 47.

Deaths by Sex

The data were grouped by quarter of death, sex and birth cohort (pre-post 1970) and analysed by Poisson regression to investigate whether the trend differs by age group or between the sexes. The results showed that although the upward trend is greater for the males, this difference is not significant (p=0.36).

Deaths by cohort

So far the age at death has not increased as might have been expected, given that most exposure to BSE ceased in the early 1990's. In order to examine this further, the cases were divided by birth cohort pre and post 1970 and the trends in deaths over time were compared between these cohorts. Figures 8 and 9 show that the trend appears to be increasing more quickly in the post 1970 cohort. However, the trends do not significantly differ (trend = 1.09 pre 1970 and 1.36 post 1970, p=0.1). This will continue to be monitored to see if further evidence of a difference emerges.

Figure 8 **Observed (-o-) quarterly incidence of vCJD deaths (pre 1970 cohort) Fitted underlying trend (___) is given with its 95% confidence limits (...)**

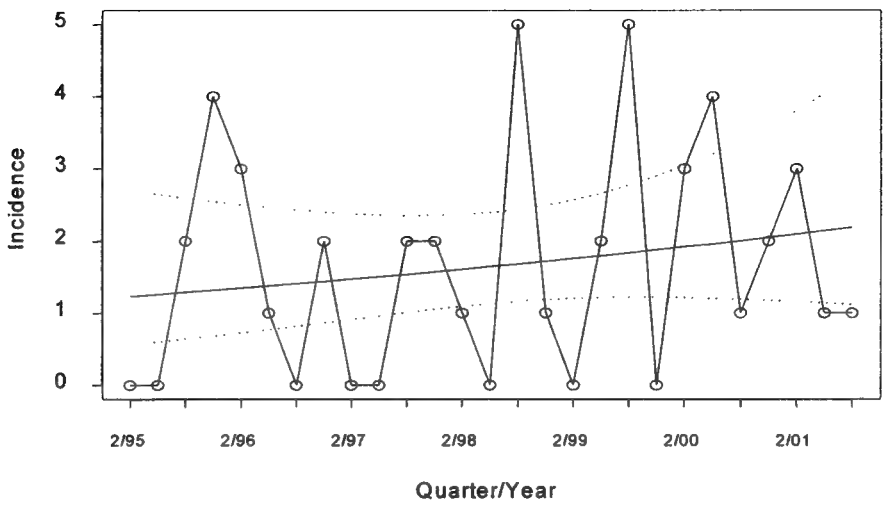
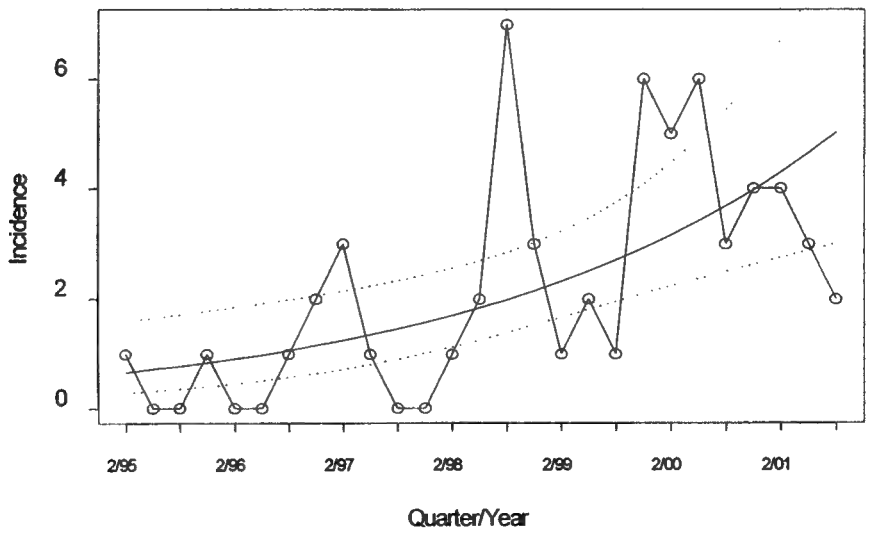


Figure 9 **Observed (-o-) quarterly incidence of vCJD deaths (post 1970 cohort) Fitted underlying trend (___) is given with its 95% confidence limits (...)**



Summary

The upward trend in vCJD cases since 1995 continues to be statistically significant with an increase of 21% per year for onsets and 23% per year for deaths. The estimated current rate of onsets is 8.3 per quarter and deaths is 7.0 per quarter. There has been a decrease in the delay from onset to diagnosis of about 5% per year. The models predict that a total of 140 onsets (95%CI: 131 to 154) had occurred by December 2001 and that in the following 12 months there will be a further 32 deaths (95%CI: 19 to 47). There is no evidence yet of a significant departure from an exponential increase in cases, however this will be monitored closely because the models with quadratic terms are consistent with an epidemic reaching its peak.

Geographical distribution of variant CJD

Figure 10 shows the geographical distribution, by place of residence at onset, of 110 cases of vCJD in the UK for whom residential information at onset is available. Cases have been widely spread throughout the UK. Table 3 presents data on the geographical distribution, by county of residence at onset, of the cases who had died by 31 January 2001 (for whom information on place of residence at onset was available) along with the crude mortality rate per million population per annum of each standard region.

Figure 10 Geographical distribution of places of residence at onset of symptoms of vCJD cases (n=110)

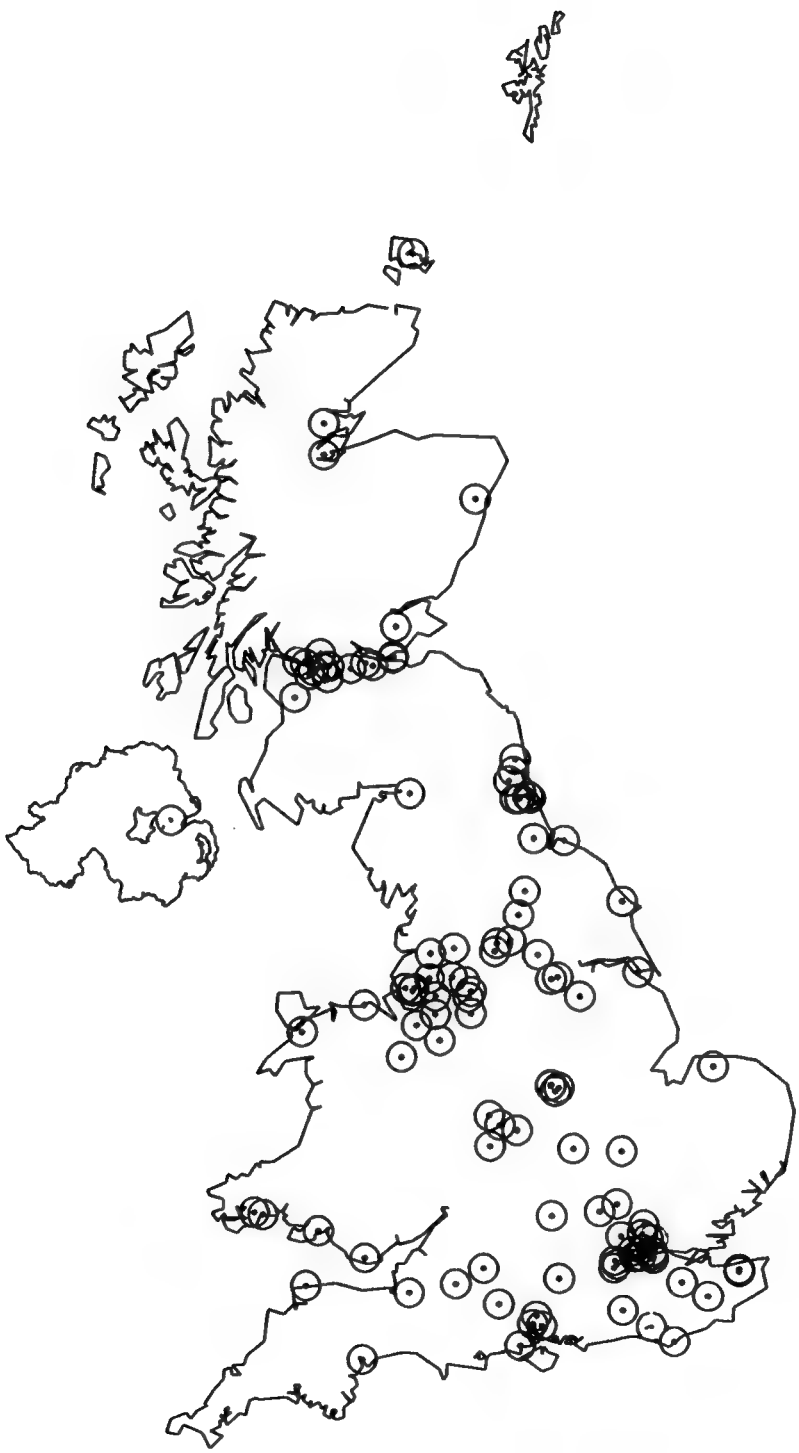


Table 3 Deaths from definite and probable vCJD by region and county of onset: 1 May 1995 - 31 January 2002

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
North		
Cleveland	2	
Cumbria	1	10 (0.48)
Durham	1	
Northumberland	2	
Tyne & Wear	4	
East Midlands		
Derbyshire	0	
Leicestershire	4	
Lincolnshire	1	6 (0.22)
Northamptonshire	1	
Nottinghamshire	0	
South East		
Bedfordshire	0	
Berkshire	0	
Buckinghamshire	0	
East Sussex	1	
Essex	0	
Greater London	9	
Hampshire	5	26 (0.22)
Hertfordshire	2	
Isle of Wight	0	
Kent	4	
Oxfordshire	1	
Surrey	3	
West Sussex	1	
North West		
Cheshire	4	
Greater Manchester	5	14 (0.32)
Lancashire	2	
Merseyside	3	
WALES		
Clwyd	1	
Dyfed	2	
Gwent	0	
Gwynedd	1	
Mid Glamorgan	0	
Powys	0	
South Glamorgan	1	
West Glamorgan	1	
TOTAL FOR WALES		**6 (0.31)**
NORTHERN IRELAND	1	**1 (0.09)**

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
Yorkshire & Humberside		
Humberside	2	
NorthYorkshire	2	
South Yorkshire	2	10 (0.29)
West Yorkshire	4	
East Anglia		
Cambridgeshire	1	
Norfolk	1	2 (0.14)
Suffolk	0	
South West		
Avon	0	
Cornwall	0	
Devon	2	6 (0.19)
Dorset	0	
Gloucestershire	0	
Somerset	2	
Wiltshire	2	
West Midlands		
Hereford & Worcs.	0	
Shropshire	1	
Staffordshire	0	3 (0.08)
Warwickshire	1	
West Mids (Met)	1	
TOTAL FOR ENGLAND		**77 (0.23)**
In an additional 3 cases, information on address at onset is not available		
SCOTLAND		
Borders	0	
Central	0	
Dumfries & Galloway	0	
Fife	1	
Grampian	1	
Highland	2	
Lothian	4	
Strathclyde	9	
Tayside	0	
Islands (Shetland)	0	
Islands (Orkney)	1	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**18 (0.52)**

* Based on 1994 population by region (ONS Regional Trends, 1996 edition) over the 6.75 year period.

Table 4 shows cumulative regional rates of vCJD based on cases' place of residence in 1991, rather than at onset, and the population aged 10 years and above resident at that time. We originally performed an analysis of the first 51 cases, distinguishing two areas. The "North" comprised four standard regions: Scotland, North, Yorkshire and Humberside, North West. The "South" comprised the remaining 6 regions: Wales, West Midlands, East Midlands, East Anglia, South West, South East.

Age- and sex- standardised "incidence" ratios (SIRs) based on cases' place of residence in 1991 are shown in Figure 11 for the 10 standard regions of Great Britain (only one case in Northern Ireland to date).

Table 4 Distribution of 110 vCJD cases by standard region of residence on 1st January 1991

Standard region (in order of latitude of the centre of the region)	Population aged 10 years and above at the 1991 census	Number (cumulative incidence/million) of vCJD cases by place of residence in 1991
Scotland	4,363,684	17 (3.90)
North	2,635,785	9 (3.41)
Yorkshire & Humberside	4,202,051	11 (2.62)
North-West	5,396,333	16 (2.96)
East Midlands	3,444,391	8 (2.32)
West Midlands	4,464,592	7 (1.57)
East Anglia	1,775,687	2 (1.13)
Wales	2,466,669	4 (1.62)
South-East	15,010,650	27 (1.80)
South-West	4,055,268	9 (2.22)
Total	47,815,110	110 (2.30)

Figure 11 Standardised incidence ratios (SIRs) up to 31st January 2001 of vCJD by standard region on 1st January 1991

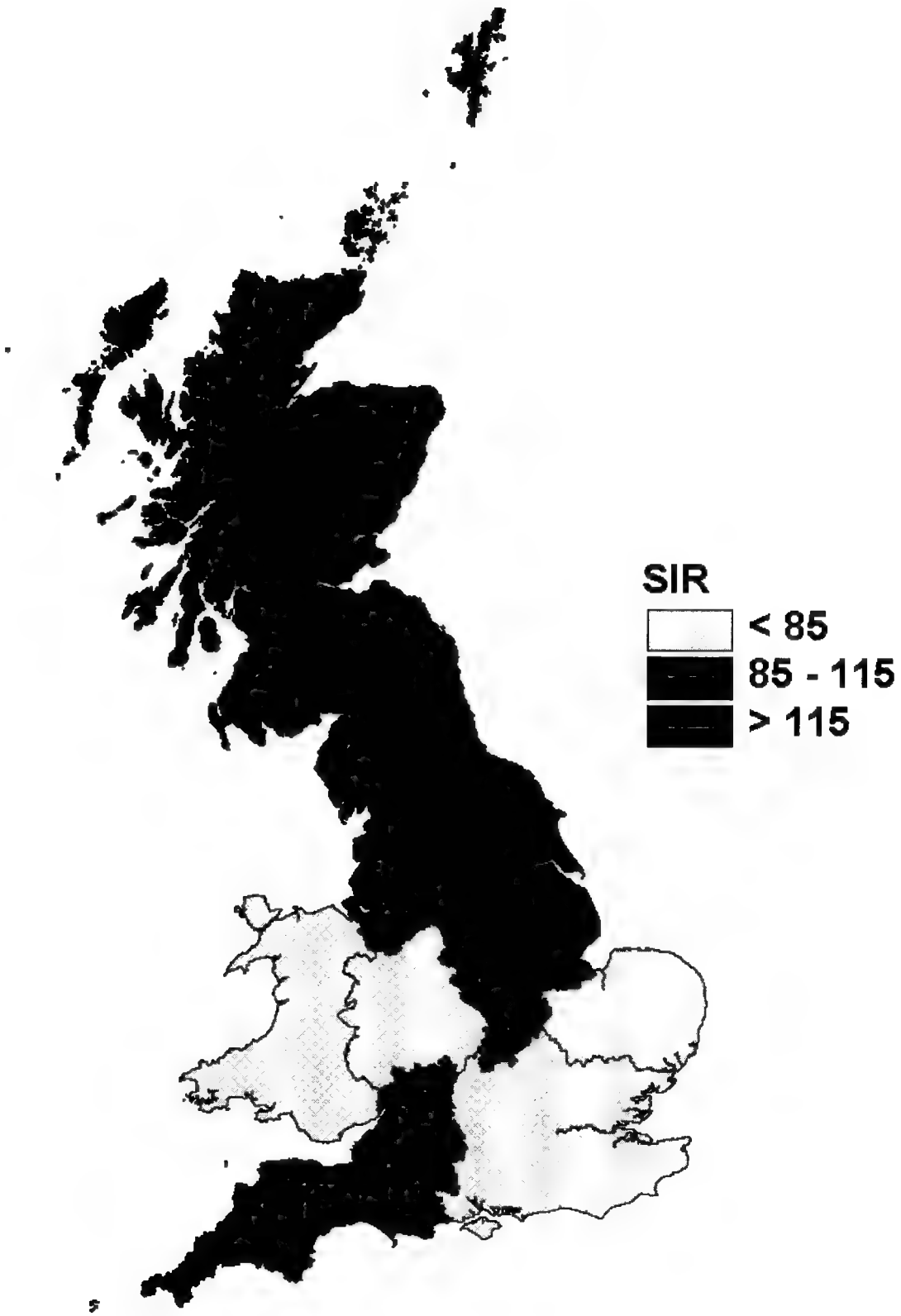


Table 5 shows the distribution of cases between the "North" and the "South" in 1991, for those cases included in the initial analysis (51) and for all cases. The excess of cases previously identified in the "North" (rate ratio controlling for age and sex = 1.94; 95% c.i. 1.12, 3.36) has been largely maintained in subsequent cases with, overall, an estimated rate ratio controlling for age and sex of 1.72 (95% c.i. 1.19, 2.50). I.e. individuals living in the "North" in 1991 are about one and three quarter times more likely to have developed vCJD than individuals who were living in the "South" in 1991.

Table 5 Comparison of cumulative incidence in the "North" of the UK (excluding Northern Ireland) with that in the "South"

Region	**Population aged 10 years and above at the 1991 census**	**Number (rate/million) of vCJD cases by place of residence at 1st January 1991**	
		First 51 cases	Total
"North" (North West, Yorks & Humbs, Northern, Scotland)	16.6 million	26 (1.57)	53 (3.19)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	31.2 million	25 (0.80)	57 (1.83)
Total (rate ratio[1])	47.8 million	51 (1.94)	110 (1.72)

Northern cases were slightly older at onset than southern cases (median of 27 years versus 24 years; p=0.4) and more of them were male (57% versus 47% of southern cases; p=0.3).

[1] North versus South, adjusted for age and sex

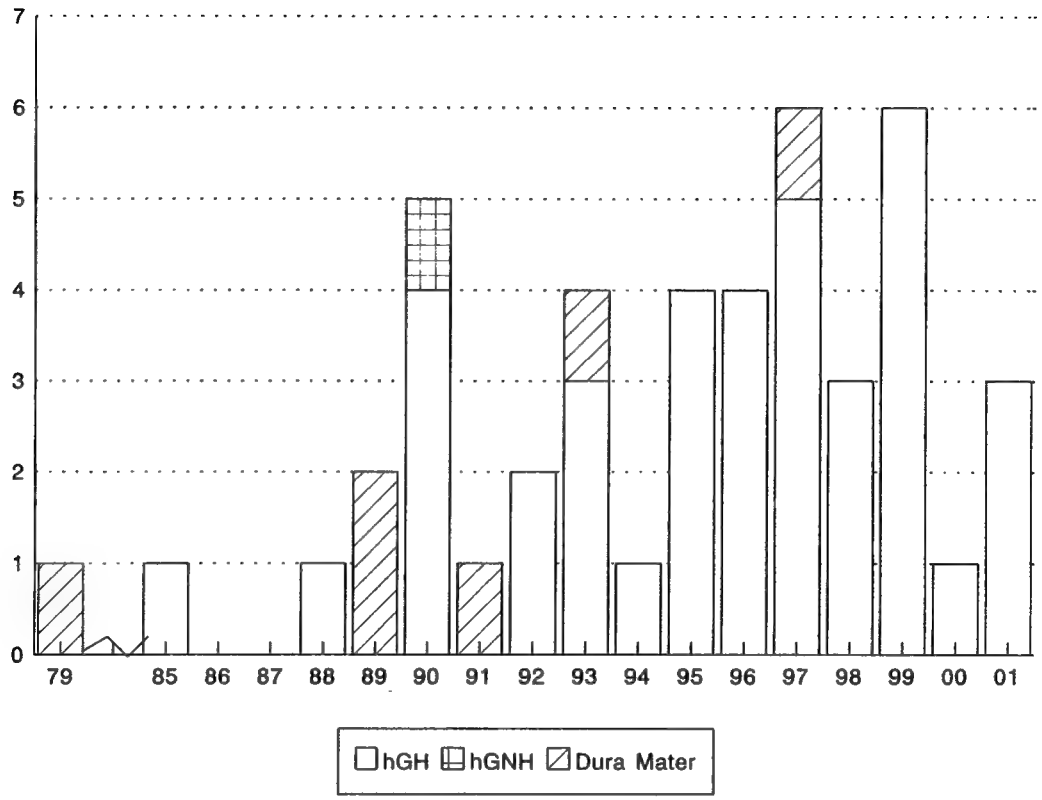
Geographically Associated Cases of variant CJD

To date, the five cases of variant CJD in Leicestershire remain the only statistically significant cluster of cases of vCJD in the UK. This cluster was investigated by Drs Monk and Bryant of Leicestershire Health Authority. The investigation identified a possible explanation for the cluster, namely meat preparation techniques used in local butchers' shops in the 1980s, which could have led to cross contamination of muscle meat with brain tissue (www.leics-ha.org.uk). Following on from the Leicestershire investigation, a national protocol was developed to investigate cases of vCJD associated with one or more other cases by residential or social geographical proximity since 1980 (www.cjd.ed.ac.uk). Nine areas in the UK with two or more geographically associated cases of vCJD have been investigated or are in the process of being investigated according to this national protocol. The investigation of five cases of vCJD who lived at some time in the Southampton area indicated that this number of cases could have arisen by chance from the population and did not constitute a statistically significant cluster (www.sswhha.org.uk). Apart from residence at some time within the Southampton area, the only common factor was the immunisation of two cases using oral polio vaccine from the same batch. The finding was thoroughly assessed and was not thought to indicate a risk of contracting vCJD from polio vaccine. These findings did not change the Committee on the Safety of Medicine's assessment of the risk of oral polio vaccine, which was that there were no demonstrable BSE safety issues arising from the use of UK bovine materials in manufacturing vaccines.

2.3 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 2001, 45 cases of CJD attributable to iatrogenic exposure have been identified, 6 in individuals receiving dura mater implants, 38 in individuals who had received human-derived growth hormone (hGH) and one in a recipient of human gonadotrophin (hGN) (Figure 12).

Figure 12 Deaths from iatrogenic CJD, 1979-2001



The mean age at death of the hGH /hGN group was 29½ years (with a range of 20-45 years) and for the dura mater cases 43 years (range 27-59 years).

The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985.

2.4 Transfusion Medicine Epidemiology Review

The Transfusion Medicine Epidemiology Review (TMER) is a collaborative project between the UK NCJDSU and UK Blood Services (UKBS). The main purpose is to investigate whether there is any evidence that CJD or vCJD may have been transmitted via the blood supply.

Methods

vCJD cases (definite and probables) are notified to the UKBS by NCJDSU; a search establishes whether any have acted as donors. Donation records are checked and all components traced through hospital records. Details of all identified recipients are forwarded to NCJDSU for subsequent checking.

In the reverse procedure, patients with vCJD reported to have received blood transfusions are identified by NCJDSU and notified to UKBS. Details of transfusions are traced through hospital records and relevant blood donors identified. The identity of donors is notified to NCJDSU for subsequent checking.

Results

Seventeen vCJD cases were reported to have been blood donors. To date, only 10 have been traced at blood centres, and 8 of these had donated blood, with a resulting 48 blood components. It has been established that 22 components were transfused to named recipients none of whom have developed vCJD to date.

In the reverse study, 8 vCJD cases were reported to have received blood transfusions. Checks revealed that 2 were not transfused, 2 had transfusions which predated available records and 4 had records of transfusion which could be traced. These 4 individuals had received 117 components of blood, which have been traced to 111 named donors (one patient received 103 components). The donors of two components are not traceable and checking is still incomplete on 4 components. None of the donors have been identified as vCJD cases.

Conclusion

No donors or recipients identified in the study through the tracing of donation and transfusion records appear in the NCJDSU register as cases. Further data on vCJD cases, to define time interval between blood donation and development of disease are being accumulated.

(Collaborators on this project: Dr P.E. Hewitt and Dr C.A. Llewelyn).

2.5 Study of Progressive Intellectual & Neurological Deterioration (PIND)

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an Expert Neurological Advisory Group of six paediatric neurologists which allocates the cases to a diagnostic category[1].

After almost 5 years surveillance, 1278 patients with suspected PIND have been reported. The Expert Group has discussed 936 cases, of which 535 have a confirmed underlying cause other than vCJD, being categorised into 93 known neurodegenerative diseases. Among them were six cases of vCJD; four definite and two probable. Three were reported in 1999, one in 2000 and 2 in mid-2001. One girl was aged 12 at onset - the youngest case of vCJD identified to date.

(Collaborators: Dr C. Verity, Dr A. Nicoll, Ms G. Devereux).

[1] Verity CM, Nicoll A, Will RG, Devereux G, Stellitano L. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. Lancet 2000; 356: 1224-1227.

SECTION 3

3. Case-Control Study

Since May 1990, a case-control study of CJD has been carried out in the UK to investigate potential risk factors. Relatives of patients with suspect CJD have been interviewed using a standard questionnaire, which includes a wide range of questions relating to putative risk factors for CJD, including residential, occupational, dietary and medical histories. Up until 1997, for each suspect case, an age- and sex-matched inpatient at the same hospital was identified as a control. At the end of 1997 the design of the study was changed. In addition to hospital controls for variant cases and instead of hospital controls for sporadic cases, community controls have been recruited, matched for sex and age ± 4 years, through general medical practices (up to 4 for each case of vCJD and one for each case of sporadic CJD). Community controls are more suitable than hospital controls for the investigation of potential medical risk factors. When possible, a relative of the same degree as for the case is interviewed using the standard questionnaire. If this is not possible the control is interviewed directly. Ethical clearance for the revised study design was received from the Multi-Centre Research Ethics Committee for Scotland in October 1998, and subsequently from 213 Local Research Ethics Committees (LREC) for each general practice in the study.

As of end of March 2002, letters have been sent to 299 GPs (relating to 102 variant cases and 197 sporadic cases) to ask them to participate in the study and 170 practices (relating to 69 variant cases and 101 sporadic cases) have been visited. Letters have been sent to 1312 potential controls for variant cases by their GP describing the study and asking them to agree to be approached directly by the NCJDSU. Three hundred and thirty-one (25%) of these individuals have replied, of whom 253 (76%) agreed to be contacted by the NCJDSU. Of those written to by the NCJDSU (n=250), 177 (71%) have replied. One hundred and seventy have consented to take part in the study and have nominated a relative for interview. One hundred and thirty-nine relatives have agreed to take part in the study, of whom 120 have been interviewed. Seventy-five community controls for sporadic cases have been interviewed.

Conditional logistic regression (Stata Statistical Software: Release 6.0) was used to examine associations between exposure to each putative risk factor and risk of CJD.

Sporadic CJD

Since 1997 risk factor questionnaires have been completed for sporadic CJD cases and community controls. Analysis of these data is likely to begin in the coming year.

Variant CJD

By the end of 2001, risk factor questionnaires for 116 community controls and 62 hospital controls had been completed (relating to 51 and 62 vCJD cases, respectively). Comparisons of cases with controls are performed separately for community and hospital control groups, because of the potential heterogeneity of these two control groups with respect to factors under investigation. For this report, an analysis comparing cases with hospital controls has not been performed, because the number of hospital controls accrued since last year's report does not merit re-analysis.

3.1 Medical risk factors for vCJD

Seventy-three percent of community controls were reported to have undergone some sort of operation/surgical procedure in the past compared with 67% of cases (Table 6). There is no evidence to suggest that particular operations/surgical procedures are associated with increased risk of vCJD (Table 6). However, the confidence intervals around these odds ratio estimates are wide. These findings should not be interpreted as evidence that transmission via surgery has never, or could never, occur.

Table 6 **Reported operations/surgical procedures for 51 cases of variant Creutzfeldt-Jakob disease and 116 community controls.**

Type of operation/ surgical procedure	% of cases (n = 51)	% of controls (n= 116)	Odds ratio (95% CI), p value (based on matched cases and controls)
Any operation	67	73	0.7 (0.3, 1.6), 0.4
Neurological operation	2	2	1.5 (0.1, 16.5), 0.7
Eye operation	2	4	0.4 (0.0, 4.1), 0.5
Ear operation	2	3	0.6 (0.1, 6.0), 0.7
Orthopaedic operation	8	11	0.7 (0.2, 2.2), 0.5
Abdominal operation*	22	17	1.4 (0.4, 4.2), 0.6
Tonsillectomy	8	14	0.7 (0.2, 2.1), 0.5
Appendicectomy	4	7	0.5 (0.1, 2.4), 0.4
Other	55	59	0.9 (0.4, 2.0), 0.9

*includes appendicectomy

Blood transfusion

5 of the 51 cases were reported by relatives to have had a history of blood transfusion compared with 6 of the 116 community controls, (O.R. 2.3 (0.7, 7.8), p= 0.2).

3.2 Dietary risk factors for vCJD

The reported consumption of various different meats and meat products by cases and controls in the period since 1980 (except for one case where the period is from 1985 due to a change in the questionnaire and one case where the relative could only answer from 1993 onwards) is shown in Table 7.

Almost all cases and community controls were reported to have eaten beef (joints, steaks, stews etc.). Ninety-two percent of cases and 96% of controls ate sausages (p=0.15), 91% and 89% ate meat pies (p=0.9) and 88% and 91% ate burgers (p=0.2) respectively. Only four controls were reported to have eaten brain. No cases or controls reported having eaten eyes. More controls (62%) than cases (38%) were reported to have eaten liver sausage (p=0.006). This result may be biased by the low case response rate (32/51) compared with controls (100%) - see footnote to Table 7. In addition, it should be remembered that because of multiple statistical testing, one

test with a p-value below 0.05 might be expected by chance from 22 tests (Table 7). Last year's report noted that more cases than controls were reported to have eaten black pudding (p=0.04), but with greater numbers in the analysis this difference has become less noteworthy (p=0.15).

Table 7 Reported consumption of different types of meat from 51 cases[1] of variant Creutzfeldt-Jakob disease and 116 community controls.

Type of foodstuff	% of cases (n =51, unless indicated)	% of community controls (n =116, unless indicated)	Odds ratio (95% C.I.); p-value (based on matched cases and controls)
Beef	100 (50)	98 (114)	∝ (0.1, ∝); 0.4
Sausages	92	96 (114)	0.4 (0.1, 1.4); 0.1
Burgers	88 (50)	91 (113)	0.5 (0.2, 1.5); 0.2
Meat pies[3]	91 (43)	89	0.9 (0.3, 3.3); 0.9
MRM[2]	96	97	0.5 (0.1, 3.2), 0.5
Venison	20	29	0.6 (0.3, 1.5); 0.3
Veal	16	28	0.4 (0.1, 1.1); 0.07
Brain	0	3 (115)	0.0 (0.0, 2.6); 0.1
Liver	49	61 (115)	0.6 (0.3, 1.2); 0.1
Kidney	29	23 (115)	1.6 (0.7, 3.8); 0.2
Sweetbreads	0 (50)	3 (115)	0.0 (0.0, 1.9); 0.07
Lamb	92	95 (115)	0.6 (0.2, 2.3); 0.5
Pork	98	98 (115)	0.8 (0.1, 10.6); 0.9
Chicken	98	97	1.2 (0.1, 11.4); 0.9
Faggots[3]	31 (45)	24 (115)	1.8 (0.7, 4.7); 0.2
Tripe	6	10 (115)	0.5 (0.1, 2.0); 0.4
Liver sausage[3]	38 (32)	62	0.2 (0.1, 0.6); 0.006
Haggis	25	32	0.7 (0.3, 1.6); 0.4
Steak tartare[3]	0 (33)	4	0.0 (0.0, 8.8); 0.4
Cheese	98	95 (115)	3.3 (0.4, 28.4); 0.3
Cows milk	100	97 (115)	∝ (0.3, ∝); 0.2
Black pudding	41	31 (114)	1.7 (0.8, 3.6); 0.2

[1] In one case the dietary history was recorded from 1985 onwards and in another from 1993 onwards. In the remainder it was taken from 1980.

[2] MRM- mechanically recovered meat- burgers, meat pies & sausages used in this analysis

[3] Low case response rates for questions on meat pies, faggots, liver sausage and steak tartare are due to early case questionnaires not including these items.

The reported frequency of consumption of the selected food items shown in Table 7 by cases and community controls were compared; some of which are shown in Table 8. There was weak evidence that the reported frequency of consumption of burgers and faggots was greater for cases compared with controls (p= 0.06 and 0.08, respectively). There was stronger evidence that the reported frequency of consumption of sausages and products which might have contained mechanically recovered meat (MRM) (derived from the combined frequencies of eating burgers, meat pies and sausages) was greater for cases compared to controls (p=0.004 and p=0.006, respectively). There was no evidence that the reported frequency of consumption of beef or meat pies differed between cases and controls (p= 0.2 and 0.7, respectively).

Table 8 Reported frequency of consumption of food items from 51 vCJD cases[1] compared with 116 community controls

Foodstuff eaten	Frequency	% of cases (n =51, unless indicated)	% of community controls (n =116, unless indicated)	Odds ratio (95% C.I.); (based on matched cases and controls)	p-value for trend
Beef	≤ 1 per month	28 (50)	25 (114)	1.0	0.2
	1 per week	18	48	0.3 (0.1, 0.8)	
	> 1 per week	54	26	1.4 (0.6, 3.5)	
Sausages	≤ 1 per month	43	62 (114)	1.0	0.004
	1 per week	33	33	1.4 (0.6, 3.0)	
	> 1 per week	24	4	8.4 (2.2, 32.5)	
Burgers	≤ 1 per year	16 (50)	23 (113)	1.0	0.06
	Several times per year to 1 per month	32	50	0.9 (0.3, 2.4)	
	≥ 1 per week	52	27	2.4 (0.7, 7.6)	
Meat pies	≤ 1 per year	21 (43)	23	1.0	0.7
	Several times per year to 1 per month	40	40	1.1 (0.4, 2.8)	
	≥ 1 per week	40	37	0.9 (0.3, 2.3)	
MRM[2]	≤ 2 per month	12	33 (113)	1.0	0.006
	2> & <8 per month	29	35	1.9 (0.7, 5.5)	
	≥ 8 per month	59	33	4.4 (1.5, 12.7)	
Faggots	Never	69 (45)	76 (115)	1.0	0.08
	≤1 per year	13	15	1.2 (0.4, 3.8)	
	> 1 per year	18	10	3.4 (0.9, 12.4)	

[1] In one case the dietary history was recorded from 1985 onwards and in another from 1993 onwards. In the remainder it was taken from 1980.

[2] MRM- mechanically recovered meat- burgers, meat pies & sausages used in this analysis

Summary

The majority of cases and community controls were reported to have eaten beef and products containing MRM. Therefore, any case-control difference is more likely to be seen in terms of the frequency of consumption. Cases were reported to have eaten sausages, burgers, faggots and products containing MRM more frequently than community controls. This is consistent with the comparison of cases with hospital controls described in last year's Annual Report, which showed that more cases ate burgers than hospital controls (p=0.02), and cases ate burgers, beef and products containing MRM more frequently than hospital controls (p=0.002, p=0.008 and p=0.07, respectively). However, care should be taken in interpreting these results as there is considerable scope for recall bias with respect to dietary histories. In addition, a large number of statistical comparisons were performed, increasing the probability of observing some "statistically significant" associations, which reflect nothing but chance.

In order to examine the possibility of recall bias in relation to dietary history, cases of vCJD (n=112) were compared with another group of controls (n=33), which consisted of people referred to the NCJDSU with suspect vCJD who were subsequently determined to have an alternative diagnosis. Cases were reported to have eaten beef, burgers and sausages more frequently than these controls (43% of cases and 36% controls ate beef more than once per week, 55% of cases and 47% of controls ate burgers at least once per week, 24% of cases and 22% of controls ate sausages more than once per week). However, these differences were not statistically significant (beef, p= 0.5; burgers, p= 0.2; sausages, p=0.6). These results do not at present allow definitive conclusions to be drawn about the presence or magnitude of any recall bias with respect to diet. They leave open both possibilities - either that the greater reported frequency of consumption by cases of various beef products is the result of recall bias, or that it reflects increased risk of vCJD associated with consumption of these items.

3.3 Occupation and variant CJD

Table 9 compares the proportions of cases and matched community controls that were reported as having ever worked in an occupation which, in terms of possible exposure, might pose a higher risk for vCJD. There is no evidence that any of the occupations considered are associated

with increased risk of vCJD, which is consistent with the results from cases compared with hospital controls in last year's Annual Report.

Table 9 Occupation of 50 vCJD cases compared with 116 community controls

Type of occupation	% of cases (n=50)	% of community controls (n=116)	Odds ratio (95% C.I.), p value (based on matched cases and controls)
Medical/ paramedical/ nursing/ dentistry	4	13	0.2 (0.0, 1.4);0.1
Animal laboratories	0	1	0.0 (0.0, 39.0); 0.3
Pharmaceutical laboratories	0	3	0.0 (0.0, 8.8); 0.4
Other research laboratories	0	2	0.0 (0.0, 13.0); 0.4
Animal farming/ veterinary medicine	6	7	1.0 (0.2, 4.2);1.0
Meat industry	10	9	0.9 (0.3, 3.1), 0.9
Catering industry	30	29	1.0 (0.5, 2.0), 1.0
Other involving animal products	2	3	0.8 (0.1, 7.3), 0.8

3.4 Conclusion

To date, we have not observed any evidence of an increased risk of vCJD associated with a reported previous history of surgical procedures or employment in an occupation that might have led to exposure to the BSE/vCJD agent. Some differences in reported diets were observed between cases and controls. These differences are difficult to interpret given the number of statistical comparisons performed and the potential for recall bias to affect interviewees' responses. Continued recruitment of cases and matched community controls will enable us to make stronger statements in the future with regard to the presence/absence of risk associated with diet, surgical procedures and occupation and the presence/absence of recall bias.

SECTION

4

Laboratory Activities

Laboratory investigations are part of the internationally-agreed diagnostic criteria for CJD, both during life (CSF protein analysis and PrP genetic studies) and post-mortem (neuropathology and protein studies). The NCJDSU has facilities to perform all of these investigations, which aid the timely and accurate diagnosis of all forms of CJD and are essential for surveillance purposes.

4.1 Neuropathology - Statement of Progress

The neuropathology laboratory in the NCJDSU continues to maintain a high workload in terms of diagnostic and research activities, including the work of the protein laboratory. The laboratory maintains close links with other neuropathology centres across the UK and overseas with scientific, medical, technical and student visitors over the past year for specialist training purposes. The laboratory has continued its major role in the National Retrospective Review of CJD and Related Disorders and in the retrospective study to detect abnormal PrP in anonymised specimens of appendix and tonsil tissue. Although in the early part of 2001 the autopsy rates for sporadic and variant CJD were maintained at a high level, these rates have declined throughout the year, in keeping with national trends which have been markedly influenced by the outcome of the Alder Hey inquiry. The NCJDSU laboratory has taken part in the national audit of retained organs following autopsy and we were inspected by Audit Scotland for this purpose in December 2001. The preliminary report following this inspection was entirely satisfactory; the complete report will be published in 2002. As before, the laboratory continues to act as a source of information to a wide range of professionals involved in health and safety issues relating to CJD. We are most grateful to all neuropathologists, general pathologists and their technical, secretarial and autopsy room staff for their continuing support of NCJDSU. We are also grateful to the relatives of patients with CJD for allowing us to study this group of devastating disorders.

4.2 Surveillance and Workload during 2001

A detailed breakdown of laboratory activities is summarised in Table 10. These demonstrate that the total number of cases referred to the laboratory from the UK has declined slightly, in keeping with the downturn in autopsy rates across the UK. As in previous years, the second most frequent alternative diagnosis for sporadic CJD is Alzheimer's disease, but a wide range of alternative diagnoses have been made. The neuropathological features of variant CJD cases have been reviewed (see publications list). This has indicated that the neuropathological phenotype of variant CJD has remained relatively constant over the past six years, and no other cases with neuropathological features similar to variant CJD were identified during 2001. The laboratory has liaised with pathologists overseas to review cases of variant CJD identified outside the UK, principally in France but also involving one patient who was investigated in Hong Kong (following a disease onset in the UK). The laboratory is a major contributor to the World Health Organisation TSE Diagnostics Working Group, and continues to act as an international reference centre for the diagnosis of CJD.

Table 10 Breakdown of Laboratory Activities
Period 1st January 2001 – 31st December 2001

	CURRENT YEAR	*PREVIOUS YEAR*
REFERRED CASES (UK)		
Sporadic CJD	44	36
Familial CJD	0	1
vCJD	17	24
Iatrogenic CJD (GHT)	0	0
Gerstmann-Straussler-Scheinker	1	0
Fatal Familial Insomnia	0	0
No evidence of CJD (no alternative diagnosis)	17	21
Alzheimer's disease	11	9
Dementia with Lewy Bodies	0	4
Other †	10	10
Peripheral Organs	0	1
Research Project (occular material)	1	0
Research Project (Nat ret post 90)	0	18
REFERRED CASES (EU)		
Confirmed CJD	9	11
vCJD	1	1
GSS	0	1
Other	8	2
Research Project	1	0
REFERRED CASES (ROW)		
Confirmed CJD	4	4
vCJD	1	0
Other	6	1
TOTAL NUMBER OF CASES	**131**	**144**

NOTES

† Other:

Widespread cerebrovascular disease	3	Multifocal demyelination	1
Giant cell arteritis of coronary artery	1	Malignant intravascular lymphoma	1
Arteriosclerosis + ischaemic damage	1	Meningioma	1
Right cerebral infarct	1		
Corticobasal ganglionic degeneration	1		

Abbreviations:

GHT: Growth Hormone Therapy
EU: European Union
ROW: Rest of World

4.3 Protein Laboratory

Prion protein isotyping is carried out as a routine diagnostic test on all suspected cases of CJD where fresh brain tissue is received by the NCJDSU. Small quantities of cerebral cortex are homogenized, treated with proteases and the size and abundance of the three PrP^{res} glycoforms determined by Western blot analysis. The prion protein isotype is classified as type 1 if the nonglycosylated form has a molecular weight of ~21kDa or type 2 if the nonglycosylated form has a molecular weight of ~19kDa. The suffix B is used to denote a PrP^{res} isotype where the diglycosylated band predominates. The remaining type 2 cases where the diglycosylated band does not predominate are termed type 2A. The type 2B isotype has previously found to be characteristic of variant CJD.

Table 11 Breakdown of cases analysed in 2001

Diagnosis	Type	PrP^{res} +ve CNS
CJD (n=25)	Sporadic	17/17
	Variant	8/8
Other (n=12)	Alzheimer disease	0/5
	Other or not determined	0/8*

* includes two brain biopsies

Genetic analysis of *PRNP* codon 129 was unavailable in 10 sporadic CJD cases and 4 variant CJD cases.

Table 12 Isotype/genotype breakdown of CJD cases analysed in 2001

Diagnosis	129	Type 1	Type 2A	Type 2B	Total
Sporadic CJD	M/M	3	0	0	3
	M/V	1	2	0	3
	V/V	0	1	0	1
	Total	4	3	0	7
Variant CJD	M/M	0	0	4	4
	M/V	0	0	0	0
	V/V	0	0	0	0
	Total	0	0	4	4

One case of sporadic CJD, of unknown codon 129 genotype was found on routine analysis to contain both type 1 and type 2 PrP^{res}. This brings the number of cases of CJD in which we have detected both types to a total of ten.

Ten requests for Western blot analysis were also received from non-UK referrals (EU 6, rest of the world 4), including four tonsil biopsies, one of which was positive.

4.4 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 2001 for collaborative research purposes with colleagues in the UK and overseas. Funding has been obtained for the appointment of a brain bank manager to start work in 2002, who will take primary responsibility for this unique resource.

4.5 Molecular Genetics

Forty-seven cases of familial CJD (excluding cases of GSS) have been identified since 1970 by the NCJDSU (these data are incomplete as formal investigation of familial CJD in the UK is undertaken by the Prion Unit at St Mary's Hospital in London). Of the 47 cases identified by the NCJDSU, 43 were resident in England and 4 were resident in Wales. Four cases are still alive. Twenty-two of the cases had insertions in the coding region of the PrP gene, 12 carried the mutation at codon 200 (Glu-Lys), 2 at codon 178 (Asp-Asn, both with methionine at codon 129, ie FFI), 1 at codon 117 (Ala-Val) and 1 at codon 210 (Val-Ile). Nine were identified as familial on the basis of relatives known to have had CJD. The mean age at death was 56 years (range 38 - 77 years).

Codon 129 distribution in sporadic CJD

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes in sporadic CJD (69% MM, 15% MV, 17% VV) (see Table 13) is consistent with findings from other European countries. There is no evidence ($p > 0.1$) of a change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-2001.

Table 13 Codon 129 genotypes of cases of sporadic CJD in the UK, 1990-2001

Deaths from sporadic CJD	MM (%)	MV (%)	VV (%)
Deaths from 1 May 1990 - 31 December 1995	95 (75)	14 (11)	17 (13)
Deaths from 1 Jan 1996 - 31 December 2001	120 (64)	32 (17)	35 (19)
Total	215 (69)	46 (15)	52 (17)
Genotype distribution for the normal caucasian population pooling data from five studies	(39)	(50)	(11)

Codon 129 distribution in vCJD

All cases for whom genetic data are available (98) were methionine homozygotes at codon 129 of the PrP gene.

The genetic laboratory undertakes genetic analysis on a national and international basis.

4.6 CSF 14-3-3 and other brain-specific proteins

Introduction

The CSF laboratory provides an international and national diagnostic service and is recognised by the WHO as an international centre for 14-3-3 analysis.

The laboratory received 223 CSF samples from January 2001 –December 2001. The origin and numbers of these samples is given in Table 14.

Table 14 Number and origin of CSF samples received at the NCJDSU during January 2001 - December 2001

Source	Number of CSF samples (% of total)
CJD patient referrals	109 (49%)
CSF only referrals	72 (32%)
Non-UK countries	42 (19%)
Total	223 (100%)

CSF 14-3-3 results in CJD patient referrals

The CSF 14-3-3 results in patients referred to the NCJDSU with suspected CJD are shown in Table 15.

Table 15 CSF 14-3-3 results in patients referred to NCJDSU during January - December 2001.

Type of CJD	Diagnostic group (number of patients)	Positive 14-3-3 / Total number samples tested	Number of blood stained CSF samples
Sporadic	Definite (8)	6/7	1
	Probable (26)	24/24*	0
	Possible (10)	1/9**	0
	Not CJD (30)	3/28***	2
Variant	Definite (2)	0/2	0
	Probable (16)	4/16	0
	Possible (1)	0/1	0
	Not CJD (12)	1/12	0
Familial	Probable (2)	1/2	0
Iatrogenic	Probable (2)	2/2	0

* Two CSF samples received were insufficient for analysis

** One CSF sample insufficient for analysis

*** For one of these patients no diagnosis was established and, although not meeting the clinical criteria for possible CJD, CJD cannot be ruled out.

Of the 24 patients with probable sporadic, 20 were classified as probable on the basis of a positive 14-3-3.

There were 2 patients with suspected sporadic with positive 14-3-3 results who were subsequently found to have another diagnosis. One had corticobasal degeneration, the other had a cerebrovascular event. A third patient with a positive 14-3-3 test result died without a post-mortem or enough clinical signs to be classified as a probable case. No alternative diagnosis was established for this individual and so CJD cannot be completely ruled out.

One patient with definite sporadic CJD had a negative CSF 14-3-3. This patient was referred after death and had a typical disease duration of 5 months.

One patient with suspected vCJD had a positive 14-3-3. After MRI investigation, a final diagnosis of acute disseminating myelitis was made.

CSF S-100b and CSF tau concentrations in CJD patient referrals

Table 16 CSF S-100b and CSF tau concentrations in patients referred in 2001 with sporadic and variant CJD. S-100b reference range: less than 0.38 ng/mL; CSF tau reference range: less than 315 pg/mL

Disease Group	CSF S-100b ng / mL (mean ± SD)	CSF tau pg / mL (mean ± SD)
Sporadic CJD		
Definite/Probable	2.17 ± 2.29	2973 ± 3079
Not sporadic CJD	0.46 ± 0.25	2454 ± 3238
Variant CJD		
Definite/Probable	0.61 ± 0.34	1418 ± 1767
Not variant CJD	0.56 ± 0.65	529 ± 422

Elevated concentrations of S-100b and tau protein were found in patients with both sporadic and variant CJD as previously reported.[1,2,3]

CSF 14-3-3 in CSF only referrals

Seventy-two CSF samples were received as CSF only referrals and constituted 32% of the total number of samples received. The CSF 14-3-3 results are shown in Table 17.

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3.Green AJE, Thompson EJ, Stewart GE, Zeidler M, Mackenzie JM, Macleod MA et al. Use of 14-3-3 and other brain-specific proteins in the CSF in the diagnosis of variant Creutzfeldt-Jakob disease. JNNP 2001; 70: 744-748.

Table 17 CSF 14-3-3 in CSF only referrals during 2001

Positive 14-3-3/ total number samples	Number of blood stained CSF samples
8/71	1

Of the 8 patients with positive CSF 14-3-3, 2 patients had Hashimoto's thyroiditis, one patient improved on steroids, one patient had a cerebrovascular event, one patient had a leukoencephalopathy, one patient stabilised and went home and no information was available for 2 other patients.

SECTION

5

National CJD Care Team

The National CJD Care team is based within the National CJD Surveillance Unit and was formed in response to concerns regarding the care of CJD patients. An initial National Care Co-ordinator post was established in February 2000 and in September 2001 the National CJD Care Team was formed with the appointment of a second Care Co-ordinator, a Neurologist (part time) and a secretary.

The role of the National CJD Care Team is to provide advice on all forms of CJD to the patients, their family and professional carers, including information on the clinical features, diagnostic procedures and prognosis. The National Care Co-ordinators are available to assist with co-ordination of care locally, by providing the necessary education and support to local health professionals involved in care of CJD patients. They are available to attend regular case conferences in order to facilitate ongoing assessment of the CJD patient's evolving care requirements. The co-ordinators are available to visit patients and their families and will provide advice on specific management issues such as symptom control. A neurologist is also available by telephone to provide advice regarding medical aspects of CJD management as well as care co-ordination issues.

When a referral has been made to the NCJDSU of a suspect case of CJD, the co-ordinator makes direct contact with the family and arranges to meet them within two weeks. Thereafter the co-ordinator meets with the patient and family on a regular basis, depending on need to provide support and is available by telephone between visits. Support continues after the patient dies.

The CJD Care Team is in close liaison with the Department of Health and provides access to the CJD Care Package, which is a sum of money available to assist with the care of CJD patients, by meeting shortfalls in the cost of services which cannot be met by local health or social service authorities. The CJD Care Team is also responsible for management of the CJD Advice

Network. This is a group of Health and Social Services Professionals who have had experience of working with CJD and are available to share their experience and provide advice.

Since the establishment of the first National Care Co-ordinator post, the co-ordinators have provided support to 40 variant CJD cases, 15 sporadic CJD cases and 4 familial cases. Currently there are 8 variant, 4 sporadic and 4 familial cases with whom the National Care Co-ordinators are in regular contact.

Table 18 Patients Alive and Visited Per Month During 2001

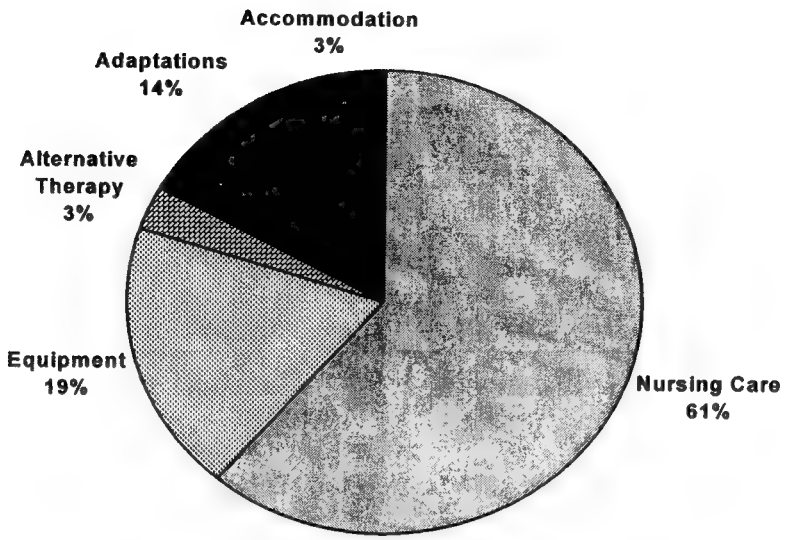
Month	Number of Patients Alive	Visited by Co-Ordinators
January	11	8
February	13	10
March	10	8
April	13	8
May*	9	3
June	11	8
July	10	5
August	11	4
September*	12	2
October	19	10
November	16	7
December*	15	4

Table 19 Case Conferences Attended/Visits by National Care Co-ordinator's during 2001

Case Conference Reference	Visits/Case Conferences		Case Conference Reference	Visits/Case Conferences
GM2	4		GM8	7
FB12	1		FB9	7
GM15	15		GM10	6
FB2	8		GM4	6
FB7	7		GM19	5
FB4	12		GM22	2
GM17	3		GM20	5
GM14	2		GM21	1
GM16	5		GM5	1
FB8	4		GM3	8
GM16	9		GM9	1
GM18	2		FB3	1
GM7	5		GM11	5
GM12	4		GM1	11

* Month during which co-ordinator was on Annual or Sick Leave

Figure 13 National Care Package Payments During 2001 (Total Budget £64,602)



SECTION

6

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SECTION 7

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Dr RSG Knight	Consultant Neurologist
Professor JE Bell	Honorary Consultant in Neuropathology
Dr H Ward	Consultant Epidemiologist
Dr B Weller	Clinical Research Fellow
Dr A Lowman	Research Registrar
Dr C Henry (to November 2001)	Research Registrar
Dr S Cooper (from December 2001)	Research Registrar
Mrs B Smith-Bathgate	Nurse Practitioner
Ms M Leitch	Research Nurse
Mr G McLean, Ms F Barnett	National Care Co-ordinators
Dr A Green	Senior Clinical Scientist
Mr M Bishop	Molecular Biologist
Ms J Mackenzie	Study Co-Ordinator
Mr A Hunter	Business Manager
Ms D Everington	Statistician
Mr N Attwood	Database Manager
Ms D Ritchie	Research Assistant
Mrs L McCardle	Chief Biomedical Scientist
Mrs M Le Grice, Ms S Lowrie and Mrs M Nicol	Senior Biomedical Scientists
Ms D Best, Ms D Auras	Research Technicians
Mrs V McLoughlin	Laboratory Technician
Dr M Head	Research Scientist (molecular and cell biology)
Ms BA Mackenzie	Neuropathology Database Manager/Secretariat
Ms S Smith, Ms A Honeyman, Mrs S Macdonald	Secretariat
Mrs M Wells (to Aug 2001)	Secretariat - Case-control study
Ms A Davies, Ms K Sewell	Secretariat - Case-control study

Staff funded by Other Sources

Dr W. Nailon (BBSRC)	Research Scientist (image analysis)
Dr N McLennan (MRC)	Research Scientist (molecular and cell biology)
Ms K Rennison (EC BIOTECH)	Research Technician
Mr T Bunn (UoE)	PhD student
Ms T Lindsay (BIOMED2)	European Study Co-Ordinator
Mrs C Donaldson (BIOMED2)	Secretariat

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Professor P Smith	Epidemiologist and Head of Dept of Infectious and Tropical Diseases
Mr S Cousens	Statistician